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Childhood Cancer Etiology: Recent Reports

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Chernobyl: The Fallout Continues

Previous reports have failed to document an increase in childhood leukemia following the Chernobyl accident. However, different forms of childhood leukemia may have different etiologies, and radiation may play different roles in each. Outside the former Soviet Union, contamination resulting from the Chernobyl accident has been highest in Greece and Austria, and also the Scandinavian countries. In a study performed in Greece, Petridou and colleagues [Nature 382:352–353, 1996] have examined the incidence of leukemia in children exposed to the Chernobyl accident while in utero. All childhood leukemia cases diagnosed throughout Greece since 1980 have been recorded by a national network of childhood oncologists and the available data include gender, date of birth, date of diagnosis, type of leukemia, and maternal residence. Exposure of the Greek population to Chernobyl ionizing radiation started soon after the accident and was detectable for about 1 year with average exposure estimated at 2 mSv. Fallout radiation from the Chernobyl accident has been measured in previous analyses in more than 1,000 samples of surface soil from 42 of the 52 administrative districts of Greece (^{137}Cs was measured) and these data were used to classify each district as high, mid, or low level exposure. For the purposes of this analysis, children born during the second half of 1986, the first half of 1987, and most of the second half of 1987 were considered to have been exposed to this low dose of irradiation in utero. Children born from 1 January 1980 to 31 December 1985 and those born from 1 January 1988 to 31 December 1990 were considered unexposed. The analysis was based on estimation of age-adjusted leukemia rates, calculated until the end of the fourth year of life. Comparison of the two unexposed cohorts showed no evidence of any difference in the incidence of leukemia. There was also no difference in the incidence of leukemia at ages 12 to 47 months between children exposed and unexposed in utero. However, infants (age less than 12 months at diagnosis of leukemia) exposed in utero had 2.6 times the incidence of leukemia compared to non-exposed infants ($P = 0.003$). Additionally, a dose response was observed; incidence was 32.2 (CI 18.9–39.5) per 10^6 person-years for those born in low radioactivity divisions (1 case), 71.4 (CI 31.2–141.3) for those born in intermediate exposure districts (7 cases), and 116.6 (CI 37.0–281.3) for those born in high activity divisions (4 cases). Irradiation of parents prior to conception had no demonstrable effect on leukemia risk in any of the studied age groups.

COMMENT

Considerable data are available supporting the contention that infant leukemias have different biology (and so likely etiology) compared with acute leukemias in older children. Genetic abnormalities at 11q23 occur with high frequency in these cases and the clinical behavior of the disease is remarkable aggressive, with poor results obtained with chemotherapy and frequent relapses occurring, even after bone marrow transplantation. Data from twin studies suggest that the early events of leukemogenesis take place in utero, in agreement with the findings of this study. This study demonstrates the importance of grouping malignancies in a biologically driven way when looking at etiology. Additionally, the levels of exposure in this study are extremely low, yet the dose response is convincing. Dosimetry of what constitutes ''safe'' radiation exposure in humans has necessarily been inexact, and has often been inferred indirectly. These data will contribute to our knowledge in this area, while emphasizing that the fetus (and hence pregnant women) are a special case.

Stella M. Davies

Radiation-Linked Thyroid Cancer in Children—Blame It on RET!

Thyroid cancer in children is extremely rare. However, since 1990 there have been several epidemiologic studies linking the accident at Chernobyl to an increased incidence of papillary thyroid carcinomas in children of the Belarus region. Interestingly, RET protooncogene activation has been identified in thyroid carcinoma cells following irradiation in vitro [Ito et al., Cancer Res 53: 2940–2943, 1995]. Rearrangements of RET occur in thyroid malignancies and have been highly specific for papillary carcinomas, which in turn are frequently associated with radiation exposure. In this study, Fugazzola et al. [Cancer Res 55:5617–5629, 1995] examined RET protooncogene rearrangement in 6 children with thyroid

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cancer who were exposed to the Chernobyl accident between the ages of 14 months and 8 years. Using Southern blot analysis, both RET and another tyrosine kinase receptor gene, TRK, were examined for rearrangements. No rearrangements were found with TRK-related sequences; however, 4 out of 6 tumors demonstrated RET rearrangements. Furthermore, in subsequent RT-PCR experiments using 3 tumors with sufficient material, 2 cases demonstrated translocations between the RET protooncogene and the ELE1 gene, while 1 case demonstrated a breakpoint yet unidentified. The authors suggest that further investigations into papillary thyroid carcinomas in children, comparing Chernobyl-exposed children to unexposed children, are needed.

COMMENT

This study was an elegantly designed series of experiments that tested the hypothesis that a radiation-linked tumor (from population studies) may manifest a genetic mutation known to be associated with irradiation studies in vitro. Three different rearrangements of RET have been identified so far, two of which are inversions localized to a small region on chromosome 10. The authors noted that other countries have reported varying levels of RET activation in sporadic papillary thyroid carcinomas (from about 3% to 6%). However, collectively, RET activation occurs in around 60% of Chernobyl tumors. Obviously, these findings argue for a more intensive investigation into the association between radiation and papillary thyroid carcinomas.

Julie A. Ross

EMF and Brain Tumors: Assessment Difficulties or Lack of Causation?

The suggestion that high electromagnetic field (EMF) exposure may increase a child's risk of cancer has generated much public concern and is particularly spurred by popular articles that describe cancer clusters near electric substations. In truth, the results of epidemiologic studies assessing the impact of EMF on childhood cancer have been inconsistent. A recent review article [Eur J Cancer Prev 4:(Supp 1)3–107, 1995] concluded that there may be an association between EMF and childhood leukemia. However, more data are needed before a link between EMF and childhood brain tumors can be established. A recent issue of the American Journal of Epidemiology [1996; 143:2] contained the long-awaited results of two large case-control studies that examined the relationship between EMF and childhood brain tumors (described below).

Preston-Martin et al. [pp. 105–119] augmented a large population-based case-control study of childhood brain tumors with a magnetic field assessment component. The child's lifetime exposure to magnetic fields in residences was assessed through measurements taken outside the home, and mapping and coding of the wiring configurations using the Wertheimer-Leeper classification. Data were collected for 298 case-control pairs living in the Los Angeles County Area. In addition, indoor measurements were done for 211 homes. Further, appliance usage was assessed via questionnaire. The authors found that increasing exposure to EMF was not associated with increased risk of developing a childhood brain tumor. However, a nonsignificant increase in risk was seen for children exposed to very high fields within the home.

In another study, Gurney et al. [pp. 120–128] assessed magnetic field exposure at the child's residences for the 3-year period up to the diagnosis date (or reference date) and during the mother's pregnancy. Magnetic field exposure was assessed by assigning Wertheimer-Leeper codes to power distribution maps drawn at each of the homes. Electrical appliance usage was assessed with a questionnaire. Complete data were available for 265 children (92 cases and 193 controls) who lived in the Seattle, Washington area. No relationship was found between brain tumor risk and EMF exposure as determined by the Wertheimer-Leeper wiring codes. Furthermore, there was no significant association found between use vs. non-use of appliances.

Immediately following the two articles are an invited commentary by Charles Poole and responses by Preston-Martin et al. and Gurney et al. The basic tenet of Poole's argument is that ''epidemiologic assessment of magnetic field exposures is still primitive.'' He suggests that information regarding appliance exposure and measures of exposure from power lines should be combined. Poole also addresses the issues of nonconcurrent control selection and impact of random digit dialing on control selection, and that the publication of these articles is the real beginning of peer review. He anticipates that much more information will be obtained from these studies.

COMMENT

There is no dispute that EMF exposure is one of the most difficult environmental exposures to assess. EMF is not usually detectable by humans and EMF exposure is ubiquitous in industrialized societies; hence it is difficult to determine who is ''unexposed'' [Bracken, Journal of Exposure Analysis and Environmental Epidemiology 3(1), 1993]. However, both of the above studies exhaustively evaluated EMF exposure with the techniques currently available. Their null findings, in addition to the inconsistencies of previous studies, suggest that increased exposure to EMF is not associated with increased risk of childhood brain tumors. However, as new EMF exposure assessment techniques are developed, the question will inevitably be considered again.

Andrine R. Swensen

Maternal Alcohol Ingestion—Epidemiology

Using data from the Children's Cancer Group, Shu et al. [JNCl 88:24–31, 1996] evaluated the relationship between infant leukemia risk and parental smoking and alcohol consumption during and in the month prior to pregnancy. The study included 203 cases of ALL, 88 of AML, and 11 other leukemias diagnosed in children 18 months of age or younger, and 558 individually matched controls. The data showed that maternal drinking during pregnancy (compared with not drinking) was associated with an odds ratio of 1.43 for ALL and 2.64 for AML. A dose-response relationship was observed for total maternal alcohol consumption during pregnancy and risk of AML. Alcohol-related risk appeared to be most pronounced for children who developed FAB-type M1 or M2 AML. Maternal smoking did not increase risk of ALL or AML.

COMMENT

This study provides interesting data regarding maternal ingestion of alcohol and AML, a possible biologic mechanism for which is discussed below. The study also further emphasizes the differences in etiology between ALL and AML, and even among different AML subtypes, underscoring the importance of studying these groups separately. A good example of this is the association of maternal marijuana use with childhood M4/M5 AML [Robison et al., Cancer 63:1904–1911, 1989]. As potential biologic mechanisms for a role of alcohol in carcinogenesis are elucidated, careful studies can be designed that combine epidemiology and biology.

Stella M. Davies

Maternal Alcohol Ingestion—Biology

Prenatal exposure to nitrosamines has been associated with childhood leukemias and brain tumors [Cancer Epidemiol Biom Prev 3:197–204, 1994; Am J Pub Health 85:249–252, 1995]. Understanding this association has been made difficult by the finding that in rodents, nitrosamines are poor transplacental carcinogens. In a brief but provocative study, Chabra et al. [Cancer Res 55: 6017–6020, 1995] administered nitrosamine to pregnant primates (Patas monkeys). They demonstrated measurable levels of O^6-methylguanine (the mutagenic lesion induced in DNA by nitrosamines) in fetal tissues, which were highest in placenta and fetal liver. Of even greater interest, the authors also showed that co-administered ethanol reduced the level of mutagenic lesions in the liver and placenta and increased levels in the remaining fetal tissues.

COMMENT

A dramatic adverse effect of high level in utero alcohol exposure has been clearly demonstrated in children with fetal alcohol syndrome. A more subtle effect has been suggested by epidemiologic studies showing an increased risk of AML [Cancer Epidemiol Biom Prev 2: 433–439, 1993; Cancer Epidemiol Biom Prev 3:457–460, 1994] and infant leukemia [Shu et al., reviewed above] with parental alcohol use. The biologic data presented in this study provides a plausible mechanism for this effect, together with an impetus to reexamine the epidemiologic data seeking an interaction between nitrosamines and alcohol ingestion.

Stella M. Davies

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